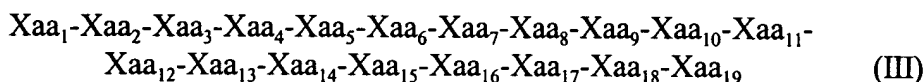
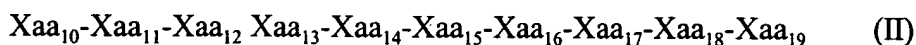
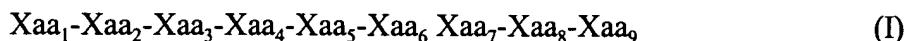


metalloproteinase-13. The invention contemplates inhibitors having amino acid sequences from the linking region of any of the matrix metalloproteinases. For example, peptide inhibitors of the invention can have amino acid sequences drawn from any region from about amino acid 70 to about amino acid 120 of the matrix metalloproteinase-2 sequence (SEQ ID NO:14), and analogous regions of all other matrix metalloproteinases.

Please substitute page 3, the paragraph beginning on line 9 and continuing on page 4 for the paragraph in the appendix entitled "Clean Version of Page 3, the Paragraph beginning on line 9." Specific amendments to page 3, the paragraph beginning on line 9 are detailed in the following marked-up paragraph:

The invention provides peptides of any one of formulae (I), (II), (III):



wherein

Xaa₁, Xaa₄, and Xaa₆ are separately each apolar amino acids;

Xaa₂ is a basic amino acid;

Xaa₃ is a cysteine-like amino acid;

Xaa₅ is a polar or aliphatic amino acid;

Xaa₇ is an acidic amino acid,

Xaa₈ is an aliphatic or polar amino acid;

Xaa₉ is an aliphatic, apolar or basic amino acid; and

Xaa₁₀ is a polar, acidic, basic or apolar amino acid;

Xaa₁₁ is a polar or aromatic amino acid;

Xaa₁₂ is a polar, basic, aliphatic or apolar amino acid ;

Xaa₁₃ is an aromatic, aliphatic, polar or acidic amino acid;

Xaa₁₄ is an aromatic, apolar or polar amino acid;

Xaa₁₅ is an apolar or acidic amino acid;

Xaa₁₆ is a basic, a polar or an apolar amino acid;

Xaa₁₇ is a basic, a polar, an aliphatic, an apolar or an acidic amino acid;

Xaa₁₈ is an apolar or an aliphatic amino acid;

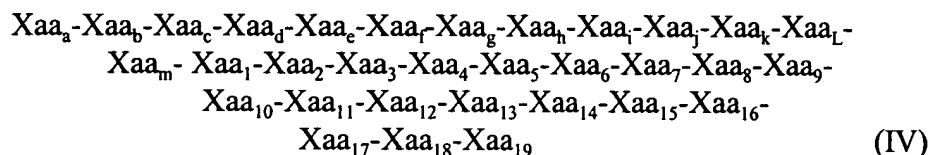
Xaa₁₉ is a basic or an aliphatic amino acid; and

wherein the peptide is capable of inhibiting the activity of matrix [metalloproteinse] metalloproteinase-1, matrix [metalloproteinse] metalloproteinase-2, matrix [metalloproteinse] metalloproteinase-3, matrix [metalloproteinse-4, matrix metalloproteinse] metalloproteinase-4, matrix [metalloproteinse] metalloproteinase-5, matrix [metalloproteinse] metalloproteinase-6, matrix [metalloproteinse]

metalloproteinase-7, matrix [metalloproteinase] metalloproteinase-8, or matrix [metalloproteinase] metalloproteinase-9, matrix [metalloproteinase] metalloproteinase-10, matrix [metalloproteinase] metalloproteinase-11, matrix [metalloproteinase] metalloproteinase-12, and matrix [metalloproteinase] metalloproteinase-13. In a preferred embodiment, the peptide can inhibit the activity of matrix [metalloproteinase] metalloproteinase-2, matrix [metalloproteinase] metalloproteinase-3, matrix [metalloproteinase] metalloproteinase-7, matrix [metalloproteinase] metalloproteinase-8, or matrix [metalloproteinase] metalloproteinase-9.

Please substitute page 5, the paragraph beginning on line 1 and continuing on page 6 for the paragraph in the appendix entitled "Clean Version of Page 5, the Paragraph beginning on line 1." Specific amendments to page 5, the paragraph beginning on line 1 are detailed in the following marked-up paragraph:

The invention also provides peptides of formula (IV) (SEQ ID NO:18):



wherein:

Xaa_a is proline;
Xaa_b is glutamine or glutamic acid;
Xaa_c is threonine;
Xaa_d is glycine;
Xaa_e is aspartic acid or glutamic acid;
Xaa_f is leucine;
Xaa_g is aspartic acid;
Xaa_h is glutamine or serine;
Xaa_i is asparagine or alanine;
Xaa_j is threonine;
Xaa_k is isoleucine or leucine;
Xaa_L is glutamic acid or lysine;
Xaa_m is threonine or alanine;

Xaa_n is methionine;
Xaa_o is arginine;
Xaa_p is lysine or threonine;
Xaa₁₇ is lysine or aspartic acid;
Xaa₁₉ is lysine; and

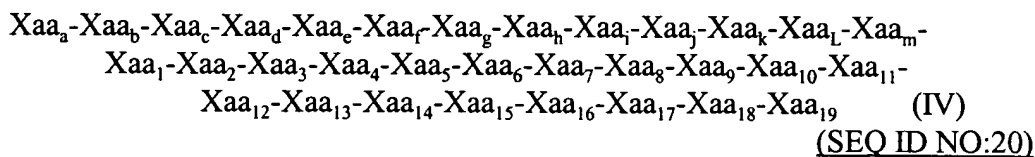
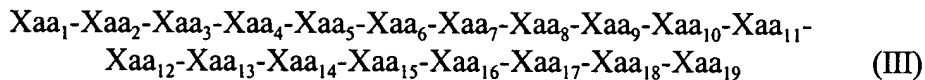
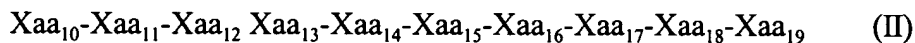
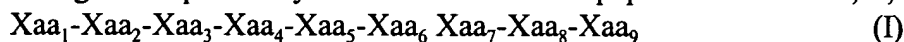
Xaa₁ is proline;
Xaa₂ is arginine;
Xaa₃ is cysteine;
Xaa₄ is glycine;
Xaa₅ is valine or asparagine;
Xaa₆ is proline;
Xaa₇ is aspartic acid;
Xaa₈ is valine or leucine;
Xaa₉ is alanine or glycine;
Xaa₁₀ is asparagine or arginine;
Xaa₁₁ is tyrosine or phenylalanine;
Xaa₁₂ is asparagine or glutamine;
Xaa₁₃ is phenylalanine or threonine;
Xaa₁₄ is phenylalanine;
Xaa₁₅ is proline or glutamic acid;
Xaa₁₆ is arginine or glycine;
Xaa₁₈ is proline or leucine;

wherein the peptide is capable of inhibiting the activity of a metalloproteinase. For

example, the metalloproteinase can be matrix [metalloproteinse] metalloproteinase-1, matrix [metalloproteinse] metalloproteinase-2, matrix [metalloproteinse] metalloproteinase-3, matrix [metalloproteinse-4, matrix metalloproteinse] metalloproteinase-4, matrix [metalloproteinse] metalloproteinase-5, matrix [metalloproteinse] metalloproteinase-6, matrix [metalloproteinse] metalloproteinase-7, matrix [metalloproteinse] metalloproteinase-8, and matrix [metalloproteinse] metalloproteinase-9, matrix [metalloproteinse] metalloproteinase-10, matrix [metalloproteinse] metalloproteinase-11, matrix [metalloproteinse] metalloproteinase-12, or matrix [metalloproteinse] metalloproteinase-13. Desirable peptides inhibit matrix metalloproteinase-2 or matrix metalloproteinase-9.

Please substitute page 6, the paragraph beginning on line 29 and continuing on pages 7 and 8 for the paragraph in the appendix entitled "Clean Version of Page 6, the Paragraph beginning on line 29." Specific amendments to page 6, the paragraph beginning on line 29 are detailed in the following marked-up paragraph:

The invention further provides a method for treating a wound that comprises administering a therapeutically effective amount of a peptide of formula I, II, III or IV :



wherein:

- Xaa₁, Xaa₄, and Xaa₆ are separately each apolar amino acids;
- Xaa₂ is a basic amino acid;
- Xaa₃ is a cysteine-like amino acid;
- Xaa₅ is a polar or aliphatic amino acid;
- Xaa₇ is an acidic amino acid,
- Xaa₈ is an aliphatic or polar amino acid;
- Xaa₉ is an aliphatic, apolar or basic amino acid; and
- Xaa₁₀ is a polar, acidic, basic or apolar amino acid;
- Xaa₁₁ is a polar or aromatic amino acid;
- Xaa₁₂ is a polar, basic, aliphatic or apolar amino acid ;
- Xaa₁₃ is an aromatic, aliphatic, polar or acidic amino acid;
- Xaa₁₄ is an aromatic, apolar or polar amino acid;

Xaa₁₅ is an apolar or acidic amino acid;
Xaa₁₆ is a basic, a polar or an apolar amino acid;
Xaa₁₇ is a basic, a polar, an aliphatic, an apolar or an acidic amino acid;
Xaa₁₈ is an apolar or an aliphatic amino acid;
Xaa₁₉ is a basic or an aliphatic amino acid;
Xaa_a is proline;
Xaa_b is glutamine or glutamic acid;
Xaa_c is threonine;
Xaa_d is glycine;
Xaa_e is aspartic acid or glutamic acid;
Xaa_f is leucine;
Xaa_g is aspartic acid;
Xaa_h is glutamine or serine;
Xaa_i is asparagine or alanine;
Xaa_j is threonine;
Xaa_k is isoleucine or leucine;
Xaa_l is glutamic acid or lysine;
Xaa_m is threonine or alanine;
Xaa_n is methionine;
Xaa_o is arginine; and
Xaa_p is lysine or threonine;

wherein the peptide is capable of inhibiting the activity of a matrix metalloproteinase.

Please substitute page 9, paragraph 2 for the paragraph in the appendix entitled "Clean Version of Page 9, Paragraph 2." Specific amendments to page 9, paragraph 2 are detailed in the following marked-up paragraph:

Figure 1 provides a CLUSTAL X (version 1.8) multiple sequence (SEQ ID NOS:2-10) alignment of the cleavage spanning regions of select MMP proenzymes. Figure 1A provides an alignment that highlights conserved residues where an '*' indicates complete identity among the sequences, a ':' indicates 7/9 conserved positions, and a '.' indicates greater than 80% identical positions with mostly conserved substitutions. Figure 1B indicates the positions of heterogeneity in bold.

Please substitute page 25, the paragraph beginning on line 9 and continuing on page 26 for the paragraph in the appendix entitled "Clean Version of Page 25, the Paragraph beginning on line 9." Specific amendments to page 25, the paragraph beginning on line 9 are detailed in the following marked-up paragraph:

In a preferred embodiment (SEQ ID NO:19):

Xaa₁ is proline,

PRELIMINARY AMENDMENT

Serial Number: 10/032,376

Filing Date: December 21, 2001

Title: METALLOPROTEINASE INHIBITORS FOR WOUND HEALING

Page 6

Dkt: 1443.008US1

Xaa₂ is arginine,
Xaa₃ is cysteine,
Xaa₄ is glycine,
Xaa₅ is valine or asparagine,
Xaa₆ is proline,
Xaa₇ is aspartic acid,
Xaa₈ is valine, leucine, or serine,
Xaa₉ is alanine, glycine or histidine,
Xaa₁₀ is asparagine, aspartic acid, histidine, arginine, glutamine or glycine,
Xaa₁₁ is tyrosine or phenylalanine,
Xaa₁₂ is asparagine, serine, arginine, glutamine, valine or methionine,
Xaa₁₃ is phenylalanine, valine, leucine, threonine, serine, or glutamic acid,
Xaa₁₄ is phenylalanine, methionine or threonine,
Xaa₁₅ is proline or glutamic acid,
Xaa₁₆ is arginine, asparagine or glycine,
Xaa₁₇ is lysine, threonine, serine, isoleucine, methionine, glycine, aspartic acid or asparagine,
Xaa₁₈ is proline or leucine, and
Xaa₁₉ is lysine, valine or arginine.

Please substitute page 27, the paragraph beginning on line 13 and continuing on page 28 for the paragraph in the appendix entitled "Clean Version of Page 27, the Paragraph beginning on line13." Specific amendments to page 27, the paragraph beginning on line 13 are detailed in the following marked-up paragraph:

In one embodiment, it is desirable to inhibit MMPs-2 and 9, but to keep the level of MMP-1 relatively unregulated in order to heal chronic wounds. Based on the sequence alignment above one of skill in the art can design a peptide with amino acids that are found in MMP2 and MMP9 proenzyme sequences but not in the MMP1 proenzyme sequence, to produce a peptide that will inhibit MMPs-2 and 9, while leaving MMP-1 uninhibited. Such a peptide is provided by formula IV.

Xaa_a-Xaa_b-Xaa_c-Xaa_d-Xaa_e-Xaa_f-Xaa_g-Xaa_h-Xaa_i-Xaa_j-Xaa_k-Xaa_L-Xaa_m-
Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Xaa₇-Xaa₈-Xaa₉-Xaa₁₀-Xaa₁₁-
Xaa₁₂-Xaa₁₃-Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉

(IV)

(SEQ ID NO:18)

wherein:

Xaa_a is proline;

Xaa_b is glutamine or glutamic acid;

Xaa_c is threonine;

Xaa₁ is proline;

Xaa₂ is arginine;

Xaa₃ is cysteine;

Xaa_d is glycine;
Xaa_e is aspartic acid or glutamic acid;

Xaa_f is leucine;
Xaa_g is aspartic acid;
Xaa_h is glutamine or serine;

Xaa_i is asparagine or alanine;

Xaa_j is threonine;
Xaa_k is isoleucine or leucine,
preferably isoleucine;
Xaa_l is glutamic acid or lysine,
preferably glutamic acid;
Xaa_m is threonine or alanine;
Xaa_n is methionine;

Xaa_o is arginine;

Xaa_p is lysine or threonine;
Xaa₁₇ is lysine or aspartic acid;
Xaa₁₉ is lysine.

Xaa₄ is glycine;
Xaa₅ is valine or asparagine,
preferably asparagine;
Xaa₆ is proline;
Xaa₇ is aspartic acid;
Xaa₈ is valine or leucine, preferably
leucine;
Xaa₉ is alanine or glycine, preferably
glycine;
Xaa₁₀ is asparagine or arginine;
Xaa₁₁ is tyrosine or phenylalanine,
preferably tyrosine;
Xaa₁₂ is asparagine or glutamine;
Xaa₁₃ is phenylalanine or threonine;
Xaa₁₄ is phenylalanine;
Xaa₁₅ is proline or glutamic acid,
preferably proline;
Xaa₁₆ is arginine or glycine,
preferably arginine;
Xaa₁₈ is proline or leucine,
preferably leucine; and

In the Claims

Please substitute the claim set in the appendix entitled "Clean Version of Pending Claims" for the previously pending claim set. Claim 28 is added and claims 5, 13, 15, 19 and 20-26 are amended. Specific amendments to individual claims are detailed in the following marked up set of claims.

Please add the following new claim:

28. (New) A composition that comprises a therapeutically effective amount of peptide of formula IV and a pharmaceutically acceptable carrier:

Xaa_a-Xaa_b-Xaa_c-Xaa_d-Xaa_e-Xaa_f-Xaa_g-Xaa_h-Xaa_i-Xaa_j-Xaa_k-Xaa_l-Xaa_m-

Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Xaa₇-Xaa₈-Xaa₉-Xaa₁₀-Xaa₁₁-

Xaa₁₂-Xaa₁₃-Xaa₁₄-Xaa₁₅-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉ (IV)

(SEQ ID NO:20)

wherein:

Xaa₁, Xaa₄, and Xaa₆ are separately each apolar amino acids;
Xaa₂ is a basic amino acid;
Xaa₃ is a cysteine-like amino acid;
Xaa₅ is a polar or aliphatic amino acid;
Xaa₇ is an acidic amino acid,
Xaa₈ is an aliphatic or polar amino acid;
Xaa₉ is an aliphatic, apolar or basic amino acid; and
Xaa₁₀ is a polar, acidic, basic or apolar amino acid;
Xaa₁₁ is a polar or aromatic amino acid;
Xaa₁₂ is a polar, basic, aliphatic or apolar amino acid ;
Xaa₁₃ is an aromatic, aliphatic, polar or acidic amino acid;
Xaa₁₄ is an aromatic, apolar or polar amino acid;
Xaa₁₅ is an apolar or acidic amino acid;
Xaa₁₆ is a basic, a polar or an apolar amino acid;
Xaa₁₇ is a basic, a polar, an aliphatic, an apolar or an acidic amino acid;
Xaa₁₈ is an apolar or an aliphatic amino acid;
Xaa₁₉ is a basic or an aliphatic amino acid;
Xaa_a is proline;
Xaa_b is glutamine or glutamic acid;
Xaa_c is threonine;
Xaa_d is glycine;
Xaa_e is aspartic acid or glutamic acid;
Xaa_f is leucine;
Xaa_g is aspartic acid;
Xaa_h is glutamine or serine;
Xaa_i is asparagine or alanine;
Xaa_j is threonine;
Xaa_k is isoleucine or leucine;
Xaa_L is glutamic acid or lysine;

Xaa_m is threonine or alanine;

Xaa_n is methionine;

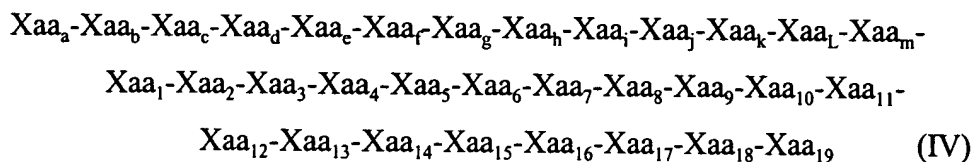
Xaa_o is arginine;

Xaa_p is lysine or threonine; and

wherein the peptide is capable of inhibiting the activity of a matrix metalloproteinase.

Please amend the following claims:

5. (Amended) A composition that comprises a therapeutically effective amount of peptide of formula IV and a pharmaceutically acceptable carrier:



(SEQ ID NO:18)

wherein:

Xaa_a is proline;

Xaa_b is glutamine or glutamic acid;

Xaa_c is threonine;

Xaa_d is glycine;

Xaa_e is aspartic acid or glutamic acid;

Xaa_f is leucine;

Xaa_g is aspartic acid;

Xaa_h is glutamine or serine;

Xaa_i is asparagine or alanine;

Xaa_j is threonine;

Xaa_k is isoleucine or leucine;

Xaa_l is glutamic acid or lysine;

Xaa_m is threonine or alanine;

Xaa₁ is proline;

Xaa₂ is arginine;

Xaa₃ is cysteine;

Xaa₄ is glycine;

Xaa₅ is valine or asparagine;

Xaa₆ is proline;

Xaa₇ is aspartic acid;

Xaa₈ is valine or leucine;

Xaa₉ is alanine or glycine;

Xaa₁₀ is asparagine or arginine;

Xaa₁₁ is tyrosine or phenylalanine;

Xaa₁₂ is asparagine or glutamine;

Xaa₁₃ is phenylalanine or threonine;

Xaa_n is methionine;

Xaa_o is arginine;

Xaa_p is lysine or threonine;

Xaa₁₇ is lysine or aspartic acid;

Xaa₁₉ is lysine; and

Xaa₁₄ is phenylalanine;

Xaa₁₅ is proline or glutamic acid;

Xaa₁₆ is arginine or glycine;

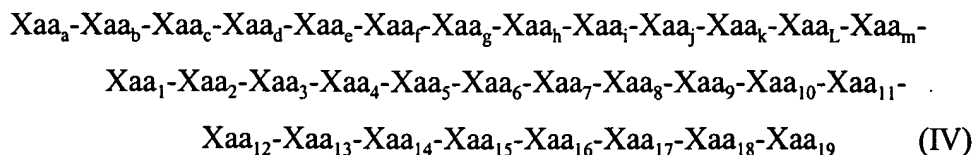
Xaa₁₈ is proline or leucine;

wherein the peptide is capable of inhibiting the activity of a matrix metalloproteinase.

13. (Amended) The composition of any one of claims 2-5 wherein the matrix metalloproteinase is any one of matrix [metalloproteinase] metalloproteinase-1, matrix [metalloproteinase] metalloproteinase-2, matrix [metalloproteinase] metalloproteinase-3, matrix [metalloproteinase-4, matrix metalloproteinase] metalloproteinase-4, matrix [metalloproteinase] metalloproteinase-5, matrix [metalloproteinase] metalloproteinase-6, matrix [metalloproteinase] metalloproteinase-7, matrix [metalloproteinase] metalloproteinase-8, and matrix [metalloproteinase] metalloproteinase-9, matrix [metalloproteinase] metalloproteinase-10, matrix [metalloproteinase] metalloproteinase-11, matrix [metalloproteinase] metalloproteinase-12, or matrix [metalloproteinase] metalloproteinase-13.

15. (Amended) The composition of claim 14 wherein the peptide can inhibit proteinase activity of any one of matrix [metalloproteinase] metalloproteinase-1, matrix [metalloproteinase] metalloproteinase-2, matrix [metalloproteinase] metalloproteinase-3, matrix [metalloproteinase-4, matrix metalloproteinase] metalloproteinase-4, matrix [metalloproteinase] metalloproteinase-5, matrix [metalloproteinase] metalloproteinase-6, matrix [metalloproteinase] metalloproteinase-7, matrix [metalloproteinase] metalloproteinase-8, and matrix [metalloproteinase] metalloproteinase-9, matrix [metalloproteinase] metalloproteinase-10, matrix [metalloproteinase] metalloproteinase-11, matrix [metalloproteinase] metalloproteinase-12, or matrix [metalloproteinase] metalloproteinase-13.

19. (Amended) A wound dressing that comprises a peptide of formula IV:



(SEQ ID NO:18)

wherein:

Xaa _a is proline;	Xaa ₁ is proline;
Xaa _b is glutamine or glutamic acid;	Xaa ₂ is arginine;
Xaa _c is threonine;	Xaa ₃ is cysteine;
Xaa _d is glycine;	Xaa ₄ is glycine;
Xaa _e is aspartic acid or glutamic acid;	Xaa ₅ is valine or asparagine;
Xaa _f is leucine;	Xaa ₆ is proline;
Xaa _g is aspartic acid;	Xaa ₇ is aspartic acid;
Xaa _h is glutamine or serine;	Xaa ₈ is valine or leucine;
Xaa _i is asparagine or alanine;	Xaa ₉ is alanine or glycine;
Xaa _j is threonine;	Xaa ₁₀ is asparagine or arginine;
Xaa _k is isoleucine or leucine;	Xaa ₁₁ is tyrosine or phenylalanine;
Xaa _l is glutamic acid or lysine;	Xaa ₁₂ is asparagine or glutamine;
Xaa _m is threonine or alanine;	Xaa ₁₃ is phenylalanine or threonine;
Xaa _n is methionine;	Xaa ₁₄ is phenylalanine;
Xaa _o is arginine;	Xaa ₁₅ is proline or glutamic acid;
Xaa _p is lysine or threonine;	Xaa ₁₆ is arginine or glycine;
Xaa ₁₇ is lysine or aspartic acid;	Xaa ₁₈ is proline or leucine;
Xaa ₁₉ is lysine; and	

wherein the peptide is capable of inhibiting the activity of a matrix metalloproteinase.

20. (Amended) The wound dressing of any one of claims 16-19 or 28, wherein an apolar amino acid is methionine, glycine or proline.
21. (Amended) The wound dressing of any one of claims 16-19 or 28, wherein a basic amino

- acid is histidine, lysine, arginine, 2,3-diaminopropionic acid, ornithine, homoarginine, p-aminophenylalanine, and 2,4-diaminobutyric acid.
22. (Amended) The wound dressing of any one of claims 16-19 or 28, wherein a cysteine-like amino acid is cysteine, homocysteine, penicillamine, or β -methyl cysteine.
23. (Amended) The wound dressing of any one of claims 16-19 or 28, wherein an aliphatic amino acid is alanine, valine, leucine, isoleucine, t-butylalanine, t-butylalanine, N-methylisoleucine, norleucine, N-methylvaline, cyclohexylalanine, β -alanine, N-methylglycine, or α -aminoisobutyric acid.
24. (Amended) The wound dressing of any one of claims 16-19 or 28, wherein an acidic amino acid is aspartic acid or glutamic acid.
25. (Amended) The wound dressing of any one of claims 16-19 or 28, wherein a polar amino acid is asparagine, glutamine, serine, threonine, tyrosine, citrulline, N-acetyl lysine, methionine sulfoxide, or homoserine, or an apolar amino acid such as methionine, glycine or proline.
26. (Amended) The wound dressing of any one of claims 16-19 or 28, wherein an aromatic amino acid is phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β -2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothieryl alanine.

Remarks

Claims 5, 13, 15, and 19 are amended. Claim 28 is added. Claims 1-28 are pending.

New claim 28 and the amendments to claims 20-26 are supported at page 7, line 9 through page 8, line 18 of the specification.

PRELIMINARY AMENDMENT

Serial Number: 10/032,376

Filing Date: December 21, 2001

Title: METALLOPROTEINASE INHIBITORS FOR WOUND HEALING

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Dkt: 1443.008US1

New claim 28 and the amendments to claims 20-26 are supported at page 7, line 9 through page 8, line 18 of the specification.

This Preliminary Amendment and the above-referenced SEQUENCE LISTING are filed to conform the above-referenced application to the requirements of 37 C.F.R. §§ 1.821 - 1.825. In accordance with 37 C.F.R. § 1.821(e), a copy of the above-submitted SEQUENCE LISTING in ASCII computer readable form is also submitted on even date herewith to U.S. Patent and Trademark Office, Box Sequence, P.O. Box 2327, Arlington VA 22202. The contents of the paper version of the SEQUENCE LISTING and the computer readable form being submitted to Box Sequence on even date herewith are the same and do not include new matter.

Respectfully submitted,

STEPHEN QUIRK

By his Representatives,

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Date Apr. 19, 2002 By Robin A. Chadwick
Robin A. Chadwick
Reg. No. 36,477

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Box Missing Parts, Commissioner of Patents, Washington, D.C. 20231, on this 19th day of April, 2002.

Name

Signature